ORIGINAL ARTICLE

Plasma biomarkers as predictors of recurrence of atrial fibrillation

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KEY WORDS

atrial fibrillation, biomarkers, recurrence of arrhythmia

ABSTRACT

INTRODUCTION Atrial fibrillation (AF) is the most common arrhythmia in the general population. There are numerous factors associated with the incidence and relapse of AF. It seems that some of them, such as neurohumoral changes, may affect AF-related atrial structural remodeling and lead to recurrence of AF.

OBJECTIVES The study aimed to assess the predictive value of plasma brain natriuretic peptide (BNP), atrial natriuretic peptide (ANP), aldosterone (ALD), and endothelin 1 (ET-1) concentrations before and after electrical cardioversion (CV).

PATIENTS AND METHODS The study included 60 patients with a dual-chamber pacemaker, persistent AF, and preserved left ventricular function who underwent successful CV. Blood samples were collected before and 24 hours and 7 days after CV. Recurrence of AF was identified by pacemaker logs lasting 30 minutes or longer.

RESULTS During a 12-month follow-up, only 5 patients (8%) had no recurrence of AF. Before cardioversion, ANP, ALD, and ET-1 levels were the same as those observed in the control group. BNP levels were significantly elevated and the level of 1237 fmol/ml or higher differentiated between patients with and without the recurrence of AF (sensitivity, 68%; specificity, 67%). Sinus rhythm restoration resulted in a significant decrease only in the BNP level. The BNP level of 700 fmol/ml or higher on day 7 after cardioversion was the most predictive for AF recurrence (sensitivity, 78%; specificity, 71%). In a multivariate analysis, only BNP levels of 700 fmol/ml or higher on day 7 after cardioversion ($P = 0.04$) and lack of amiodarone ($P = 0.03$) were independent predictors of AF recurrence.

CONCLUSIONS A BNP level of 700 fmol/ml or higher 7 days after cardioversion is an independent predictor of AF recurrence during 12 months after cardioversion. ANP, ALD, and ET-1 levels at baseline or 7 days after cardioversion are not predictive of AF recurrence.

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INTRODUCTION Atrial fibrillation (AF) is the most common arrhythmia across the general population.[1] There are several clinical factors associated with the incidence and relapse of AF.[2-4] In recent years, much attention has been paid to neurohumoral factors in the context of upstream therapy of AF. The role of the renin–angiotensin–aldosterone system (RAAS) in AF promotion has been documented,[5] and it was shown that AF leads to the activation of the neurohumoral system even in subjects without left ventricular (LV) dysfunction.[6-10] AF is characterized by a fast irregular ventricular rate, loss of atrial systolic function, and increase in atrial pressure. With elevated intracardiac pressure, stretched cardiac cells release atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and endothelin 1 (ET-1).[11,12] ET-1 affects the RAAS by stimulating aldosterone (ALD) secretion[13] and increases the release of natriuretic peptides, while these peptides inhibit ET-1 secretion.[12-14] High activity of angiotensin II, ET-1, and ALD promotes cardiac fibrosis,[6,15] thus participating in the pathophysiology of AF through atrial structural remodeling.

The aim of the present study was to assess whether plasma levels of ANP, BNP, ALD, and

ET-1 predict recurrence of AF in patients with preserved LV systolic function and with a dual-chamber pacemaker implanted, who underwent external cardioversion for persistent AF. If the predictive value of these biochemical parameters was confirmed, they would become useful in patients with persistent AF in whom it is unclear whether to choose rhythm control or rate control as treatment approach. Modern dual-chamber pacemakers are equipped with special diagnostic functions enabling detection and intracardiac recordings of AF episodes. It gives a unique opportunity to monitor cardiac rhythm and provides detailed information about AF occurrence.

PATIENTS AND METHODS The study group consisted of patients with persistent nonvalvular AF, and no significant LV systolic dysfunction, who were implanted with a dual-chamber pacemaker equipped with AF detection functions and referred for electrical cardioversion (CV). The exclusion criteria were as follows: moderately or severely depressed global LV systolic function (LV ejection fraction <45% on echocardiography before CV), clinically significant valve disease or prosthetic valve, New York Heart Association (NYHA) class III or IV heart failure, myocardial infarction, unstable angina, percutaneous coronary intervention or coronary artery bypass grafing within the preceding 3 months, or acutely reversible causes of AF. The control group consisted of 17 subjects matched for age and sex, with no history of AF or any cardiovascular disease. None of the patients were taking spironolactone or eplerenone at the time of the study.

Electrical CV was performed in patients on appropriate anticoagulant therapy based on laboratory monitoring under short-lasting general anesthesia with the use of direct-current biphasic shock (Medtronic Physio-Control Lifepak 20E, Redmond, United States) synchronized with the R-wave of the electrocardiogram (ECG). The initial shock energy was 100 J. It was increased to 200 J, and 200 J was repeated in the case of CV failure. Shocks were applied to patients with paddles localized in the anterolateral position at least 10 to 15 cm away from the pacemaker can. Before and shortly after CV, the pacemaker battery, pacing, and sensing parameters were controlled. The success of CV was defined as persistence of sinus rhythm within 24 hours after CV. The study protocol was approved by the local ethics committee and all patients gave their written informed consent to CV and participation in the study.

Study protocol All patients included in the study were examined within 24 hours before CV and then 24 hours and 7 days after CV. Medical history, physical examination, standard ECG, pacemaker control with a detailed analysis of data logs and stored ECGs as well as the measurement of plasma ANP, BNP, ALD, and ET-1 levels were performed. The main endpoint was evidence of AF episode lasting 30 minutes or longer after CV. Before CV, the percentage of pacing in the atrium (%AP) and in the ventricle (%VP) was calculated based on patients' medical records using the number of paced beats obtained during the last 3 control visits. The mean %AP and %VP were computed for each patient by calculating the mean of these values.

Follow-up control visits were scheduled at 1, 3, 6, and 12 months after CV to assess sinus rhythm control and device performance. At each visit, interrogation of the pacemaker data logs was performed. Patients were asked to go to the hospital in the case of arrhythmia symptoms, and AF was documented using standard ECG or pacemaker-derived electrograms. Recurrence of AF was defined as any AF episode lasting 30 minutes or longer recorded in the pacemaker data logs and confirmed with intracardiac recordings. Depending on the time of the first recurrence, patients were divided into 3 groups: those with AF recurrence within 30 days after CV (group 1), patients with AF recurrence between the 31 day and 1 year after CV (group 2), and patients with no AF during 1-year follow-up after CV (group 3).

Biochemical tests Blood samples were collected in patients from the study group about 2 hours before CV and 24 hours and 7 days after CV and once in subjects from the control group. Blood samples were drawn from a cubital vein in a fasting state and supine position after a resting period of 30 minutes. Tubes were centrifuged for 20 minutes at 4°C, and the plasma was stored at –70°C until the assay. Plasma ANP, BNP, ALD, and ET-1 concentrations were determined by the immunoenzymatic method using standard laboratory techniques according to the manufacturer's instructions. We used ANP No. CSB 11193h kits, Cusabio Biotech CD Ltd, China (values expressed in pg/ml), BNP No. BI-20852 kits, Biomedica, Austria (values in fmol/ml), ALD No. EIA-20052 kits, DRG International Inc, USA (values in pg/ml), and endothelin1-21 No. BI-20052 kits, Biomedica, Austria (results in fmol/ml). Patients with an episode of AF within the first 7 days after CV were excluded from the analysis.

Statistical analysis Data were presented as mean and standard deviation or number and percentage of patients. For continuous variables with normal distribution, the *t* test for independent samples was used. If variables did not follow normal distribution, the Mann–Whitney test was used for comparisons of independent measurements. The Kruskall–Wallis test or 1-way analysis of variance (ANOVA) was used for the comparison of multiple groups depending on whether data fit the assumptions of normality. Differences between categorical variables were tested with the χ^2 test. The Kaplan–Meier analysis was performed on the cumulative AF recurrence-free rate. We drew a receiver-operator characteristic (ROC) curve and a calculated area under the curve (AUC) to investigate the clinical value of the studied parameters.

TABLE 1 Clinical characteristics of patients depending on the time of the first atrial fibrillation recurrence after electrical cardioversion

Variable		Group 1 AF between 1 week and 30 days after CV (n = 28)	Group 2 AF between 31 days and 1 year after CV (n = 19)	Group 3 no AF within 1 year after CV (n = 5)	*P* value
age, y		76 ±6 (67–85)	75 ±7 (60–90)	75 ±14 (54–88)	0.9
sex, males		15 (54)	10 (53)	5 (100)	0.2
AF episode duration before CV, d		52 (6–104)	49 (37–87)	58 (6.0–71)	0.9
AF history, y		4.7 (2.8–7.3)	4.2 (2.7–9.5)	1.7 (0.9–1.9)	0.04
pacing indications	sick sinus syndrome	15 (54)	10 (53)	3 (60)	1.0
	2nd or 3rd degree atrioventricular block	13 (46)	9 (47)	2 (40)	1.0
atrial pacing, %		66 ±31	67 ±29	67 ±35	0.4
ventricular pacing, %		57 ±18	53 ±17	55 ±26	0.5
hypertension		23 (82)	18 (95)	5 (100)	0.6
coronary artery disease		9 (32)	7 (37)	2 (40)	1.0
heart failure		10 (36)	11 (59)	1 (20)	0.3
diabetes		9 (32)	7 (37)	3 (60)	0.5
chronic obstructive pulmonary disease		4 (14)	4 (21)	0 (0)	0.9
left ventricular ejection fraction		54 ±6 (46–65)	55 ±5 (46–62)	58 ±6 (52–64)	0.4
left atrial diameter, mm		47 ±3 (40–53)	46 ±3 (43–53)	48 ±5 (43–53)	0.2
left atrial area, cm^2		29 ±4 (23–38)	28 ±4 (21–40)	31 ±5 (28–41)	0.4
right atrial area, cm^2		25 ±4 (20–36)	26 ±4 (18–32)	27 ±5 (22–33)	0.4
antiarrhythmic drugs					
class 1		4 (14)	2 (11)	1 (20)	0.8
class 3		10 (36)	7 (37)	5 (100)	0.02
β-blockers		23 (82)	15 (79)	3 (60)	0.6
ACEIs or ARBs		18 (64)	12 (63)	4 (80)	0.9
statins		23 (82)	16 (84)	5 (100)	0.7

Data are shown as the number (percentage) of patients, mean ± standard deviation (interquartile range), or median (interquartile range).

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARBs – angiotensin II receptor blockers; others, see **TABLE 1**

The ROC curve was performed to test the best cut-off for prediction of AF relapse. We used the repeated-measures ANOVA to compare changes in the levels of consecutive neurohumoral factors between groups 1, 2, and 3 of patients with different time of the first AF recurrence after CV. A Cox proportional hazard analysis was performed to identify determinants associated with AF recurrence after CV using 20 variables (age, sex, AF history, AF episode duration before CV, LV ejection fraction, medication, and plasma levels of ANP, BNP, ALD, and ET-1 before CV and 24 hours and 7 days after CV). Variables with a *P* value of 0.2 or less in a univariate analysis were included in a stepwise multivariate analysis. A *P* value of less than 0.05 was considered statistically significant. The STATA software (version 12.1, STATA-Corp) was used to calculate statistics.

RESULTS Sixty patients, mean age 75 ±7.5 years, with persistent AF of median 51 days, in whom successful CV was performed were included in the study. There were no adverse events related to CV or anesthesia nor pacemaker malfunction after CV. The majority of patients (86%) had hypertension. The other risk factors of AF occurrence were coronary artery disease (34%) and diabetes (39%). Heart failure, mainly of NYHA class I, was reported in 45% of the patients. The mean LV ejection fraction was 55% ±5% and left atrial diameter was 46 ±4 mm.

Plasma BNP levels before CV were significantly higher in the study group than in the control group: 1612 ±785 fmol/ml vs 731 ±278 fmol/ml (*P* <0.001). There was a tendency for a higher ALD level before CV: 114 ±84 pg/ml vs 73 ±40 pg/ml in the control group (*P* = 0.09). No differences were found between the patient and control groups in baseline ANP or ET-1 concentrations. Plasma BNP levels decreased significantly 24 hours after CV when compared with the baseline value (*P* <0.001) and did not change further until day 7 after CV. A nonsignificant decrease (*P* = 0.09) was observed in ET-1 concentrations 24 hours after CV, with no

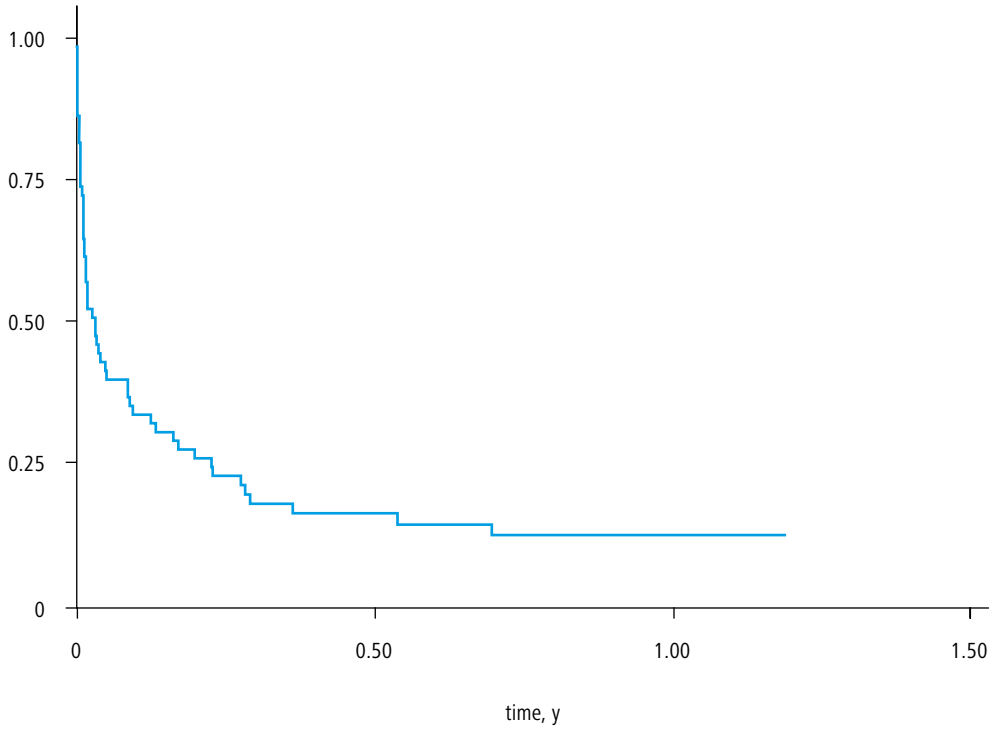

FIGURE 1 Recurrence-free rate of atrial fibrillation after electrical cardioversion

further change 7 days after CV. There were no differences in ANP and ALD concentrations after CV when compared with baseline levels.

After successful CV, AF recurred in all but 5 patients AF (FIGURE 1). In 36 patients, AF relapsed during the first 30 days after CV (group 1); in 19 patients, it recurred between day 31 and 1 year after CV (group 2); and only in 5 patients (8%), there were no documented AF episodes within 12 months after CV (group 3). Eight patients from group 1 had AF recurrence within the first week after CV, and they were excluded from the analysis. Comparing the clinical characteristics of patients in the 3 groups (TABLE 1), those with no AF within 1 year after CV had a shorter AF history and were all treated with class 3 antiarrhythmic drugs.

Plasma BNP levels before CV (BNP I) of 1237 fmol/ml or higher differentiated between patients with and without AF recurrence during follow-up with a sensitivity and specificity of 68% and 67%, respectively. The AUC for BNP I was 0.75; 95% confidence interval [CI], 0.59–0.91 (FIGURE 2A). The most predictive for AF recurrence was the BNP concentration on day 7 after CV (BNP III). The cut-off value of BNP III of 700 fmol/ml or higher predicted AF recurrence with a sensitivity and specificity of 78% and 71%, respectively. The AUC for BNP III was 0.83; 95% CI, 0.62–1.00 (FIGURE 2B).

When we compared the changes in the levels of neurohumoral factors after CV in the 3 groups (TABLE 2), the only differences were lower ANP (P = 0.045) and ET-1 (P = 0.046) and borderline lower BNP levels (P = 0.07) before CV in subjects with no AF relapse during 12-month follow-up (group 3), compared with patients with AF recurrence (group 1 or 2). Among the examined neurohumoral factors, only the changes in BNP levels were significant when comparing changes between consecutive BNP measurements (P <0.01) and the trend of changes (P = 0.07) among the 3 groups of patients (FIGURE 3). We found no other significant differences in ANP, ALD, and ET-1 concentrations between groups 1, 2, and 3.

We performed the Cox proportional hazard analysis using 20 variables (age, sex, AF history, AF episode duration before CV, medications, and plasma concentrations of ANP, BNP, ALD, and ET-1) with the endpoint being AF recurrence after CV (TABLE 3). In the univariate analysis, lower LV ejection fraction, BNP III of 700 fmol/ml or higher, and lack of amiodarone use were associated with a higher risk of AF relapse after CV. When included in the stepwise multivariate analysis, only BNP III levels of 700 fmol/ml or higher (P = 0.04) and no amiodarone treatment (P = 0.03) were independent predictors of recurrent AF.

DISCUSSION In our study, performed in patients with persistent AF and preserved LV systolic function, we found that after sinus rhythm restoration only the levels of BNP but not of ANP, ALD, or ET-1, are useful for predicting AF recurrence. Conversion to sinus rhythm resulted in a significant decrease only in BNP levels. Plasma BNP I levels of 1237 fmol/ml or higher and BNP III levels of 700 fmol/ml or higher identified patients at a risk of AF relapse. The BNP level of 700 fmol/ml or higher on day 7 after CV was the most predictive factor of AF recurrence during the 12-month follow-up. Neither the baseline levels of ANP, ALD, or ET-1 nor the changes in their levels within 7 days after CV were predictive of long-term sinus rhythm maintenance in patients with persistent AF.

The study group belongs to a larger group of patients in whom the significance of the plasma levels of neurohumoral factors in relation to AF

TABLE 2 Comparison of plasma levels of neurohumoral factors in the study groups depending on the time of the first atrial fibrillation recurrence after electrical cardioversion

Variable	Group 1 AF between 1 week and 30 days after CV (n = 28)	Group 2 AF between 31 days and 1 year after CV (n = 19)	Group 3 no AF within 1 year after CV (n = 5)	*P* value
ALD I, pg/ml	106 ±88 (0.05–391)	123 ±75 (33–279)	133 ±97 (37–272)	0.4
ALD II, pg/ml	120 ±123 (0.05–476)	129 ±78 (17–294)	117 ±93 (35–268)	0.4
ALD III, pg/ml	125 ±90 (0.05–307)	125 ±77 (44–343)	135 ±75 (87–263)	0.9
ANP I, pg/ml	106 ±12 (89–125)	114 ±24 (87–194)	95 ±6 (91–105)	0.045
ANP II, pg/ml	105 ±14 (88–143)	113 ±19 (91–168)	102 ±9 (89–113)	0.3
ANP III, pg/ml	111 ±39 (46–236)	112 ±14 (91–135)	101 ±16 (86–128)	0.3
BNP I, fmol/ml	1526 ±733 (397–3482)	1899 ±869 (666–3420)	1095 ±388 (571–1544)	0.07
BNP II, fmol/ml	1279 ±708 (326–2899)	1334 ±789 (141–2839)	709 ±430 (373–1206)	0.2
BNP III, fmol/ml	1246 ±818 (393–2986)	1329 ±595 (525–2328)	669 ±417 (385–1386)	0.2
ET-1 I, fmol/ml	1.2 ±1.3 (0.3–7.8)	1.7 ±2.0 (0.2–10)	0.5 ±0.2 (0.2–0.8)	0.046
ET-1 II, fmol/ml	1.2 ±1.3 (0.3–7.6)	1.4 ±1.7 (0.4–7.5)	0.6 ±0.3 (0.3–1.1)	0.1
ET-1 III, fmol/ml	1.2 ±0.9 (0.3–3.3)	1.1 ±0.9 (0.2–3.5)	0.5 ±0.2 (0.1–0.7)	0.1

Plasma blood samples were obtained before (I), 24 hours (II) after, and 7 days (III) after successful CV of persistent AF.

Abbreviations: AF, atrial fibrillation; ALD, aldosterone; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; CV, cardioversion; ET-1, endothelin 1

recurrence has been examined. We investigated a group of patients with a dual-chamber pacemaker implanted. Diagnostic functions and intracardiac recordings obtained from these devices enable an accurate prediction of AF relapse. In previous studies, the recurrence of AF after CV was assessed at different intervals of follow-up visits: after 4 weeks,[16] on day 30,[5,6,8,15,16] at 6 months,[17] at 1 year,[18] or after 18 months.[9] Moreover, in our study, all measurements were performed using an enzyme-linked immunosorbent assay, which is associated with a fewer limitations compared with a radioimmunological assay used in most other studies.[19]

Previous studies showed that plasma ANP and BNP levels are increased in patients with AF,[20-22] and it was reported also in patients without heart failure[7,9] and in subjects with lone AF.[23,24] Loss of effective hemodynamic atrial contraction during AF leads to elevation in atrial pressure, which subsequently increases the wall tension and results in ANP and BNP secretion from the granules in the atria. Increased atrial wall tension stimulates also the BNP gene expression in ventricles,[25] and this de novo synthesis in ventricular cardiomyocytes is of major importance in patients with LV dysfunction.[22,26,27] After sinus rhythm restoration, a significant decrease in ANP and BNP levels was noted, and it was observed even within a few hours following successful CV.[22,28-30]

Data on the predictive value of ANP and BNP concentrations in relation to sinus rhythm maintenance in patients with preserved LV systolic function are conflicting. Lellouche et al.[18] showed that elevated baseline BNP levels were an independent predictor of AF recurrence at 1 year in 66 patients with an LV ejection fraction of 53% ±12% who underwent CV for persistent AF. On the contrary, in a study performed in 43 patients with an LV ejection fraction of 53% ±6%, Wożakowska-Kapłon et al.[9] found that neither baseline BNP nor baseline NT-proANP levels[8] had a prognostic value for sinus rhythm maintenance after CV. In our patients with persistent AF, as in other studies,[7,9] BNP concentrations before CV were significantly higher in comparison with subjects with sinus rhythm. Plasma BNP levels decreased significantly within 24 hours after CV, and an increased BNP concentration on day 7 after CV was an independent predictor of AF recurrence in our group during the 12-month follow-up. Some authors consider BNP to be independently associated with AF and strongly determined by LV function for which it is an independent marker.[27] In our group, heart failure was present in 45% of the patients, but 82% of them were classified as NYHA class I, and only in 6 patients the LV ejection fraction was below 50% (and above 45% in all of them). As none of our patients presented either severe heart failure symptoms or significant LV dysfunction, we might consider changes in the BNP level as resulting from AF itself. However, we cannot exclude the influence of impaired LV diastolic function, which was not examined in our patients. Bakowski et al.[20] reported icreased plasma ANP and BNP levels in patients with preserved LV systolic but impaired LV diastolic function, and indicated that natriuretic peptides, especially BNP, may be useful in diagnosing LV diastolic dysfunction in patients with AF.

In contrast to other studies,[7,8,20] we found no differences in ANP concentrations when we compared baseline ANP with the results obtained in control subjects, and between ANP levels before and after CV. We also showed no differences in ANP levels between the 3 groups of patients with different time of AF recurrence after CV (groups 1, 2, and 3). There is no clear explanation for this; however, our patients were older (mean age, 75 years), 86% of them had arterial hypertension, and 34% had coronary artery disease with an enlarged left atrium (mean left atrial diameter, 46 mm; left atrial area, 29 cm^2). We cannot exclude that the presence of structural changes in the atria may be responsible for the observed results. Lower ANP concentrations were reported in patients with AF of longer duration,[31] which

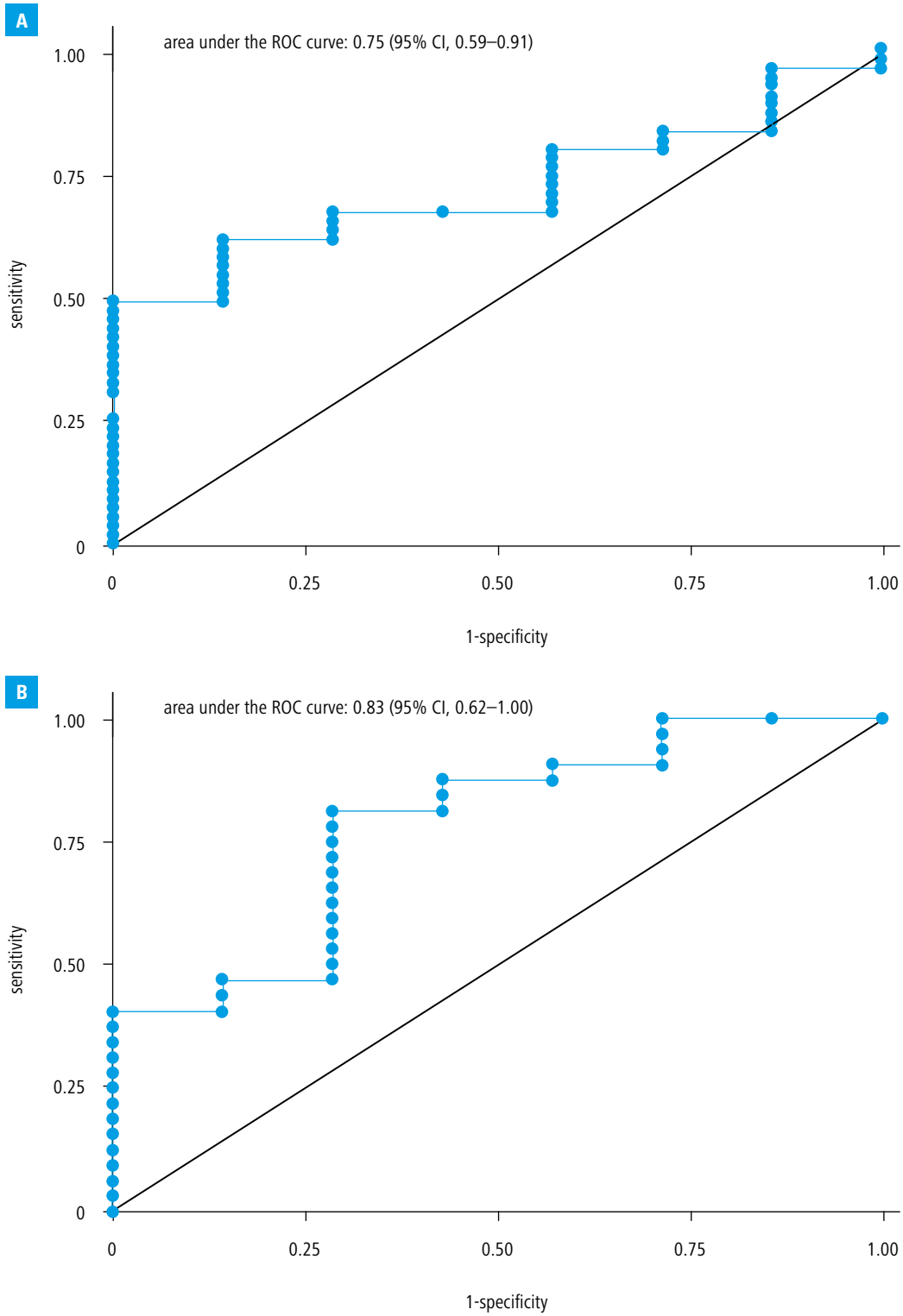

FIGURE 2 Receiver-operator characteristic curves of brain natriuretic peptide (BNP) concentration before electrical cardioversion (CV) (A), and BNP level 7 days after CV, used to separate patients with or without atrial fibrillation recurrence (B)
Abbreviations: CI, confidence interval; ROC, receiver-operating curve

may suggest inability of the atria to produce ANP in the case of degenerative structural changes. In another study, a decrease in the ANP secretion reserve of atrial cardiomyocytes during exercise in patients with persistent AF predicted CV failure and AF recurrence during a 6-month follow-up.[17]

Natriuretic peptides are neurohumoral factors that due to their vasodilatatory, natriuretic, and antimitogenic properties counteract the effects of sympathetic system and RAAS stimulation induced by AF. In contrast to natriuretic peptides, ALD and ET-1 stimulate cardiac fibrosis, thus consequently facilitating atrial structural remodeling during AF. ET-1, an endothelium-derived vasoconstrictive peptide, was reported to shorten the action potential duration in atrial myocytes.[32-34] It influences the RAAS through the stimulation of ALD release and induces cardiac hypertrophy.[35,36] Van Wamel et al.[11] reported ET-1 release by stretched cardiac cells: endothelial cells, and also by cardiomyocytes, cardiac fibroblasts, and vascular smooth muscle cells. There are little data regarding the ET-1 concentration in relation to AF recurrence, especially in patients with preserved LV systolic function. Nakazawa et al.[37] evaluated ET-1 in 51 patients with symptomatic paroxysmal/persistent AF, with no structural heart disease, who underwent pulmonary vein

TABLE 3 Predictors of atrial fibrillation recurrence after electrical cardioversion in patients with persistent atrial fibrillation

Variable	Univariate analysis		Multivariate analysis	
	HR (CI 95%)	*P* value	HR (CI 95%)	*P* value
age, y	0.99 (0.96–1.03)	0.9		
sex, male = 1	0.83 (0.48–1.44)	0.5		
AF history, y	0.98 (0.92–1.05)	0.7		
AF episode duration before CV, d	1.41 (0.40–4.96)	0.6		
LVEF, %	0.95 (0.88–0.10)	0.05	0.95 (0.88–1.03)	0.2
ANP I, pg/ml	1.01 (0.99–1.02)	0.3		
ANP II, pg/ml	1.00 (0.98–1.02)	0.9		
ANP III, pg/ml	1.01 (0.99–1.03)	0.4		
BNP I, fmol/ml	1.00 (0.99–1.00)	0.8		
BNP II, fmol/ml	1.00 (0.99–1.00)	0.4		
BNP III ≥700 fmol/ml	2.73 (1.27–5.85)	0.01	2.42 (1.01–5.79)	0.04
ALD I, pg/ml	0.997 (0.994–1.01)	0.1	0.996 (0.991–1.00)	0.2
ALD II, pg/ml	0.998 (0.998–1.00)	0.3		
ALD III, pg/ml	1.00 (0.998–1.00)	0.7		
ET-1 I, fmol/ml	0.94 (0.79–1.11)	0.4		
ET-1 II, fmol/ml	0.93 (0.75–1.16)	0.5		
ET-1 III, fmol/ml	1.29 (0.91–1.82)	0.15	1.35 (0.92–1.99)	0.1
ACEIs/ARBs	0.74 (0.41–1.33)	0.3		
β-blockers	0.98 (0.52–1.84)	0.9		
amiodarone	0.42 (0.20–0.85)	0.02	0.36 (0.15–0.89)	0.03

Abbreviations: HR, hazard ratio; LVEF, left ventricular ejection fraction; I, before CV; II, 24 hours after CV; III, 7 days after CV; others, see **TABLES 1** and **2**

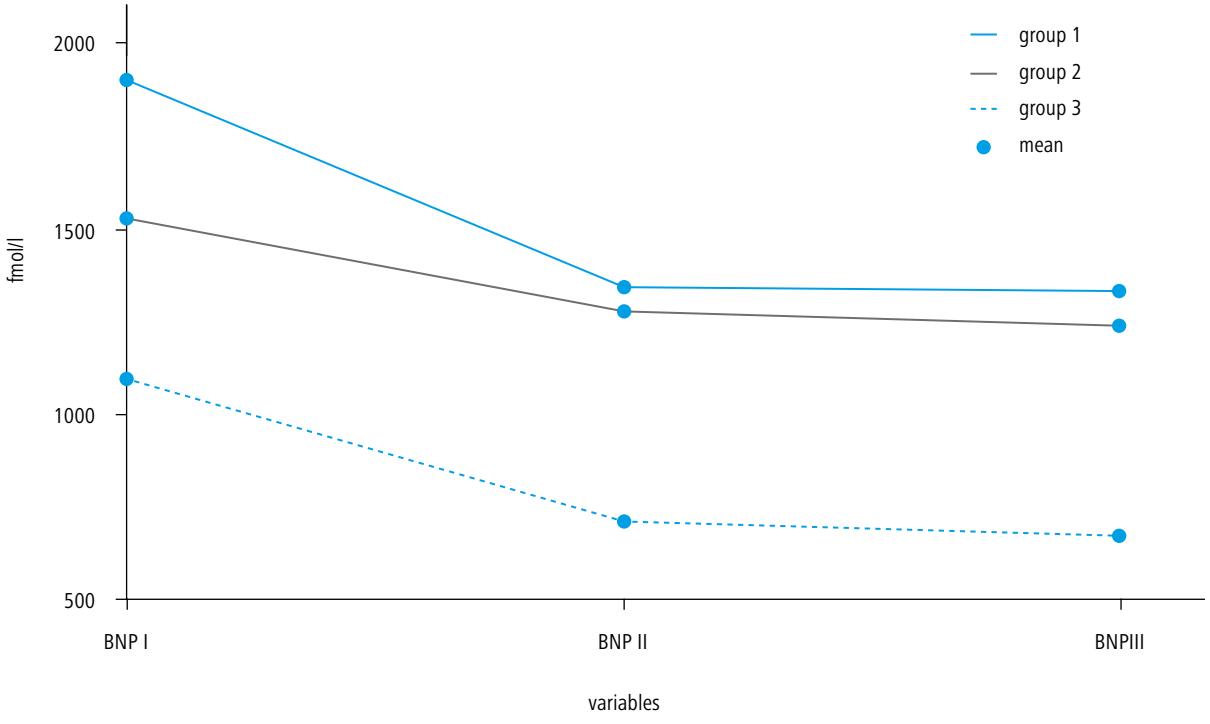

FIGURE 3 Plasma brain natriuretic peptide (BNP) concentration measured before (I) and 24 hours (II) and 7 days (III) after electrical cardioversion (CV) of persistent atrial fibrillation (AF) in the groups of patients with different time of the first AF recurrence after CV: group 1, AF recurrence ≤30 days after CV; group 2, AF recurrence between 31 days and 1 year after CV; group 3, no AF recurrence within 1 year after CV; $P < 0.01$ for comparison between BNP levels; $P = 0.07$ for comparison between groups 1, 2, and 3

isolation (PVI). Plasma ET-1 levels before PVI were significantly higher in patients with AF recurrence during 3 to 6 months after PVI compared with the nonrecurrence group, and higher ET-1 levels were a significant prognostic predictor of AF relapse. In our study, baseline ET-1 levels did not differ significantly compared with control subjects. Plasma ET-1 levels did not change significantly within 7 days after successful CV, and ET-1 concentrations did not predict AF relapse after CV. Our results are consistent with those reported by Wozakowska-Kaplon et al.[38] who examined ET-1 in patients with persistent AF and normal LV systolic function before and 24 hours after CV. As in our study, they found no differences in ET-1 levels compared with the control group or differences in ET-1 levels 24 hours after CV vs baseline.

In our study, we also examined changes in ALD levels. ALD is a factor with a number of proarrhythmic activities in relation to AF, such as volume retention, cardiac hypertrophy and fibrosis, enhanced potassium and magnesium excretion, and noradrenaline reuptake inhibition.[15] In our patients, ALD levels were insignificantly higher than in the control group. We found no differences in ALD concentrations measured after CV. There were also no differences in ALD levels between groups 1, 2, and 3 with the different time of AF recurrence after CV, and ALD concentrations did not predict AF relapse after CV during the 12-month follow-up.

Increased plasma ALD levels[39] as well as higher ALD-receptor expression were found in the atria of AF subjects.[40] In a study on 20 patients with persistent AF and preserved LV function (LV ejection fraction, 52% ±4%), Goette et al.[39] showed that ALD levels decreased significantly 48 hours after successful CV. Similarly to our study, Wożakowska-Kapłon et al.,[10] in a group of patients with persistent AF and normal LV systolic function, found that baseline ALD levels were higher than in subjects with sinus rhythm, but it did not reach statistical significance. Contrary to our results, in their group, ALD levels decreased significantly 24 hours after CV, and there was a positive correlation between a decrease in ALD levels 24 hours after CV and maintenance of sinus rhythm during 30 days of follow-up.

Study limitations The limitations of the study include a relatively small study population and a small number of patients in the group with no AF recurrence after CV during follow-up. The control group consisted of age- and sex-matched subjects with no AF or any cardiovascular disease; however, it would be more appropriate if they additionally had a dual-chamber pacemaker implanted. In our study, AF of 30 minutes or longer was used as a criterion of arrhythmia recurrence, which may seem relatively long; however, we considered it reasonable considering diagnostic possibilities of the pacemakers. Moreover, LV diastolic function was not assessed in our patients, and this issue has been raised in the discussion. Almost 70% of the patients were treated with angiotensing-converting enzyme inhibitors or angiotensin receptor blockers and it might have affected the levels of neurohumoral factors.

Conclusions The BNP level is increased in patients with persistent AF with preserved LV systolic function. Sinus rhythm restoration results in a significant decrease in BNP levels, but the BNP level of 700 fmol/ml or higher on day 7 after CV is an independent predictor of AF recurrence. Baseline ANP, ALD, or ET-1 concentrations as well as their changes within 7 days after conversion to sinus rhythm did not predict AF recurrence during the 12-month follow-up. These data were obtained with the accurate monitoring of AF recurrence by means of dual-chamber pacemaker diagnostic functions.

Contribution statement EL, JD-G, and AD-K conceived the idea for the study. ES and AL contributed to the design of the research. All authors were involved in data collection. DK and PZ analyzed the data. GR coordinated funding for the project. All authors edited and approved the final version of the manuscript.

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Biomarkery osoczowe jako predyktory nawrotu migotania przedsionków

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SŁOWA KLUCZOWE

biomarkery, migotanie przedsionków, nawroty arytmii

STRESZCZENIE

WPROWADZENIE Migotanie przedsionków (*atrial fibrillation* – AF) jest najczęstszą arytmią w populacji ogólnej. Istnieje wiele czynników odpowiedzialnych zarówno za wystąpienie, jak i nawroty AF. Wydaje się, że niektóre z nich (np. zmiany neurohumoralne) mogą wpływać na przedsionkowy remodeling strukturalny i powodować nawroty AF.

CELE Badanie miało na celu określenie, przed i po kardiowersji AF, stężenia mózgowego peptydu natriuretycznego (*brain natriuretic peptide* – BNP), przedsionkowego peptydu natriuretycznego (*atrial natriuretic peptide* – ANP), aldosteronu (ALD) i endoteliny-1 (ET-1) w osoczu oraz ustalenie ich roli w przewidywaniu nawrotu arytmii.

PACJENCI I METODY Do badania włączono 60 chorych z implantowanym dwujamowym stymulatorem serca, przetrwałym AF i zachowaną funkcją skurczową lewej komory, którzy przeszli udany zabieg kardiowersji elektrycznej. Próbki krwi do oznaczania stężenia biomarkerów pobierano przed kardiowersją oraz 24 h i 7 dni po zabiegu. Nawrót arytmii określano przy użyciu funkcji holterowskich stymulatora, ustalając kryterium trwania AF ≥30 minut.

WYNIKI Podczas 12-miesięcznej obserwacji jedynie 5 chorych (8%) nie miało nawrotu AF. Stężenie ANP, ALD i ET-1 przed kardiowersją było takie samo w grupie badanej jak w grupie kontrolnej. Stężenie BNP było natomiast istotnie podwyższone, a wartość ≥1237 fmol/ml różnicowała chorych z nawrotem i bez nawrotu AF (czułość 68%, swoistość 67%). Przywrócenie rytmu zatokowego powodowało istotne obniżenie jedynie stężenia BNP. Poziom BNP ≥700 fmol/ml w 7. dniu po kardiowersji był istotnym predyktorem nawrotu AF (czułość 78%, swoistość 71%). W analizie wieloczynnikowej BNP ≥700 fmol/ml w 7. dniu po kardiowersji ($p = 0,04$) oraz niestosowanie amiodaronu ($p = 0,03$) było niezależnym czynnikiem nawrotu AF.

WNIOSKI Stężenie BNP ≥700 fmol/ml w 7. dniu po kardiowersji jest niezależnym czynnikiem ryzyka nawrotu AF w ciągu 12 miesięcy po kardiowersji. Stężenia ANP, ALD i ET-1 zarówno przed, jak i w okresie 7. dni po kardiowersji nie pozwalają przewidywać ryzyka nawrotu AF.

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